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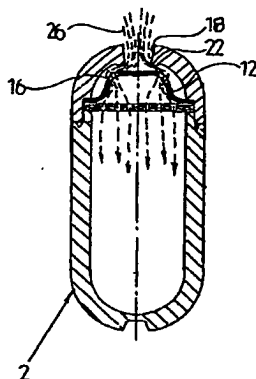
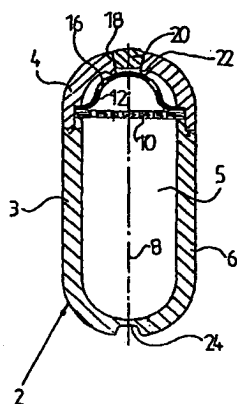
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[Continued on next page]

(54) Title: SAMPLING DEVICE AND METHOD FOR OBTAINING SAMPLES OF INTERNAL BODY SUBSTANCES AND METHOD FOR PRODUCING A SAMPLING DEVICE



(57) Abstract: The present invention relates to a sampling device and a method for obtaining samples of internal body substances in the digestive system of humans or animals. The sampling device has the shape of a swallowable capsule (2), which allows a sample of the body substance (26) to enter the capsule through an inlet opening (18). The inlet opening (18) is opening in a predetermined position of the digestive tract following contact with the body substance to be collected. The capsule (2) comprises an inner chamber disposed to preserve a substantial negative pressure when the inlet opening (18) is sealed. When the inlet opening (18) has been opened, a blocking member (12) admits flow of body substance into an inner chamber as long as there is a pressure difference between the inner chamber (5) and the external environment of the capsule (2).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Sampling device and method for obtaining samples of internal body substances and method for producing a sampling device

Field of the invention

5 The present invention relates to a sampling device for obtaining samples of internal body substances in the digestive system of humans or animals. The sampling device has the shape of a swallowable capsule which allows a sample of the body substance to enter the capsule through an inlet opening which is opened in a predetermined position of
10 the digestive tract following contact with the body substance to be collected. The invention also relates to a sampling method for obtaining samples of internal body substances and a method for producing the sampling device.

15 **Background of the invention**

Examination of internal body substances, gases or solid particles in the digestive system or the gastrointestinal tract in the human or animal body provides essential medical information for diagnosing and treatment. Examination of a sample of the gastric fluid of a patient provides important information of pH, acid contents, abdominal enzyme
20 activity as well as information for diagnosing gastric ulcer and gastritis, cancer and tumour diseases, etc. A gastroscopic examination gives the physician who is treating a patient important information and plays a great role for a diagnosis. These intubation examinations are thus used
25 extensively. A gastroscopic examination, in which a tube, having a diameter of a little finger, is inserted into the patient's mouth or nose, through the oesophagus and to the gastrointestinal system, is difficult to perform and demands the assistance of a physician. For the patient, the intubation of the digestive tract using these methods is a very unpleasant intervention, both physically and psychologically, especially
30 during the insertion of the tube and also when it is pulled out. The intubation demands that the patient is given a local anaesthetic and in

some instances even tranquilliser or a general anaesthetic to overcome the stress to which the patient is subjected. The intubation examination methods described above are disadvantageous since they are very time-consuming for a qualified physician and thus expensive and a very unpleasant intervention for the patient.

The application of a swallowable capsule for automatically obtaining samples of internal gastric fluids has been proposed as an alternative examination method and is described in US-A-4,481,952. The capsule is equipped with mechanisms, which control the opening and closing of the capsule. The mechanisms are blocked by blocking mechanisms, including a mass which is dissolved after a short time following contact with the gastric fluid. The opening of the capsule, the collection of the sample and the reclosing of the capsule takes place automatically in the patient's stomach. The described sampling device is advantageous in many ways. However, it has proved to function unsatisfactorily and has therefore not been widely used. The described capsule is expensive, is mechanically complicated and comprises mutually movable parts, mostly metal parts. As a consequence, the parts tend to jam, fluids tend to leak between the parts, friction forces between the parts must be overcome, e.g. by spring forces, and metal parts, such as springs, may loosen in the gastrointestinal tract causing injuries to the patients.

Basic idea of the invention

The object of the present invention is to solve the above-mentioned problems of the prior art by providing a sampling device which operates automatically in the system of a patient and which is simple, inexpensive to produce, reliable and easy to use.

This object is achieved in accordance with the invention in a sampling device and a method for obtaining samples and a method for producing a sampling device as described above and with the characterising features as defined in the attached claims.

In accordance with the invention, a sampling device for automatically obtaining samples of internal body substances is shaped as a capsule such that it may be swallowed by the patient without any stress or pain. In a predetermined position in the digestive system, the capsule is
5 opened and a sample of the body substance is aspirated through an inlet opening into the capsule by the force of a vacuum or substantial underpressure in the capsule. When a predetermined volume of the sampling substance has been collected in the capsule, i.e. the capsule is filled, the inlet opening is automatically closed, sealing it from the in-
10 side of the capsule, such that the sample remains in the capsule. The capsule with the collected sample is fed through the gastrointestinal tract of the digestive system and, still with no stress or pain for the patient, out of the human body together with the fecies in a normal manner. The capsule with the collected sample subsequently is sent or
15 handed over to a medical institution or laboratory, where the sample is evacuated from the capsule to be analysed.

The sampling device according to the invention is simple and is made of a few essential parts. Just one of these part, the elastic blocking member, is resiliently movable between a flow permitting con-
20 figuration and a flow preventing configuration and is affected by forces ensuing from the pressure difference between the outside and the inside of the capsule. Through this constructional feature of the closing member, a reliable, simple and inexpensive sampling device is achieved with no metal or mutually movable parts that may jam, leak or come
25 loose in the system and cause injuries to the patient. Through the production method according to the invention a vacuum or substantial underpressure is created in the capsule and this vacuum or substantial underpressure exerts sufficient forces for opening the closing member and for aspiration of a sample of a body substance into the capsule.
30 Through the sampling method according to the invention, the collection of internal body substances can be performed extremely simple and in-

expensive and the examination may be carried out without any pain, stress or discomfort to the patient.

Short description of the drawings

5 The invention will be described more in detail below with reference to the attached drawings, in which:

Figure 1 is a sectional view of a sampling device according to a first embodiment of the invention, in a first closed and sealed state,

10 Figure 2 shows the sampling device of Figure 1 in a second, open state, and in a flow permitting configuration with the body substance flowing into the device,

Figure 3 shows the sampling device of Figure 1 in a third, reclosed state, and in a flow preventing configuration in which the body substance has filled up the sampling device,

15 Figure 4 shows the sampling device of Figure 1 in a fourth, evacuating state, in which the sample of body substance is evacuated from the capsule to be analysed,

Figure 5 is a sectional view of a sampling device according to a second embodiment of the invention, in a first closed and sealed state,

20 Figure 6 shows the sampling device of Figure 5 from above,

Figure 7 shows an enlarged scale perspective view of an embodiment of the blocking member, and

Figure 8 shows a schematic elevation view of the vacuum chamber.

Detailed description of embodiments of the invention

25 Figure 1 is a sectional view of a sampling device according to the invention, said device being designed to obtain samples of internal body substances, such as body fluids, in the digestive tract of a patient. In Figure 1, the sampling device is shown in a first closed and sealed state, 30 in which it is handed over to be swallowed by a patient, from whom a sample of an internal body fluid, such as the gastric fluid in the stomach, for example, shall be collected.

The sampling device has the shape of a capsule 2, such as a conventional pharmaceutical capsule, and is thus suitable for ingestion. The capsule 2 is preferably elongated and has rounded end portions and preferably a circular or oval-shaped cross-section. The capsule 2
5 comprises an inner chamber 5 defined by a capsule wall 3.

The capsule 2, preferably made of a thermoplastic material or any other suitable material, is made of at least two capsule members, a cap member 4 and a body member 6, said cap 4 and body 6 members being permanently joined to each other, as will be described more in detail
10 below. The inner chamber 5 of the capsule 2 may comprise a filter 10, preferably clamped in the capsule 2 between the cap member 4 and the body member 6, to filtrate the body fluid sample, when required.

A blocking member 12 in the capsule is shown in an enlarged view in Figure 7. The inner blocking member 12, such as a membrane valve,
15 made of a flexible, elastic and resilient rubbery material, has a circular fixation edge 19 which is clamped in the capsule 2 between the cap member 4 and the body member 6. In the embodiment as shown, the blocking member 12 has the form of a bulb and has at least one, preferably several, apertures 16 arranged in the slanted side of the bulb. In
20 the closed and sealed state, as shown in Figure 1, the blocking member 12 bears on a preferably circular contact surface 22 on the inside of the capsule wall 3. The contact or sealing area 17 on the blocking member 12 is shown between the dashed lines in Figure 7. Through the shape of the blocking member and the resilience of the material, the blocking
25 member 12 bears on the contact surface 22 with a bearing pressure.

The circular contact surface 22, formed as a bulge-formed lining, is arranged on the inside of the capsule wall 3 and extends around an inlet opening 18 in said wall. In the closed and sealed state of the capsule as shown in Figure 1, the inlet opening 18 is sealed by a plug 20.
30 The plug 20 in the capsule 2 is made of a material which is chosen depending on the application of the capsule, i.e. the specific body fluid to be collected. The plug 20 is dissolved after a short period of time in the

body fluid in question, in the embodiment as described, the digestive fluid. Thus, the material of the plug 20 is adapted to the specific fluid or substance in the external environment of the capsule in the position in the body system where the sample is collected. The material of the plug 5 20 is, for example, gelatine, molten sugar, salt, glue, organic edible materials or any other suitable material. Alternatively, the plug 20 can be made of two or more layers of different materials, which dissolve gradually upon contact with different substances in the external environment of the capsule 2 during its passage through the digestive system. 10 The innermost layer dissolves upon contact with body fluid to be collected by the capsule 2.

A section of the capsule wall 3, preferably in the body member 6 of the capsule, is thinner and forms a notch 24. The notch 24 is used when the body fluid sample in the inner chamber 5 shall be evacuated 15 from the capsule, as will be described more in detail with reference to Figure 4.

In the inner chamber 5 of the capsule, defined by the capsule wall 3 and the plug 20, a vacuum or substantial underpressure prevails as long as the capsule 2 is in the closed and sealed state as shown in 20 Figure 1.

When an examination of a body fluid in the digestive system is required, the patient swallows the capsule 2, e.g. the capsule as shown in Figure 1, without any stress or pain. The size of the capsule 2 may vary depending on the volume of body fluid required for the examination and 25 analysis. A suitable size of a capsule which is easy to swallow has, for example, a length of about 25 mm and a width of about 10 mm.

In Figure 2, the inlet opening 18 of the capsule 2 has been opened. When the capsule is in the state as shown in Figure 2, the capsule has previously been swallowed by the patient, has passed the oesophagus 30 and has entered into the stomach. During the passage of the capsule 2 from the mouth to the position in the system of the patient in which the sample shall be collected, the patient feels no more discomfort than he

feels when he swallows an ordinary pharmaceutical capsule, i.e. a discomfort which is principally non-existing.

When the plug 20 has been dissolved, as shown in Figure 2, the inlet opening 18 is open. A suction effect is generated by the pressure difference between the external environment of the capsule 2 and the inner chamber 5 in which a vacuum or substantial underpressure prevails. This suction effect forces the resilient blocking member 12 into a flow permitting configuration, as shown in Figure 2. The body fluid 26 in the external environment of the capsule flows into the inlet opening 18 and exerts a pressure on the resilient and elastic, self-sealing blocking member 12, such that a fluid passage into the chamber 5 is opened between the contact surface 22 and the blocking member 12. The body fluid 26 flows further through the apertures 16 in the blocking member 12, through the filter 10, if any, and into the inner chamber 5, as shown in Figure 2.

The blocking member 12 is opened and is kept open by the pressure difference between the external environment of the capsule and the inner chamber of the capsule 2. As soon as the external and internal pressure of the capsule have been equalised and the body fluid 26 has filled up the inner chamber 5 of the capsule, the blocking member 12 reverts to a flow preventing configuration, such that the inlet opening 18 is closed and thus the flow of body fluid from the inner chamber 5 of the capsule is prevented. This reclosed state of the capsule is shown in Figure 3. Since the body fluid sample fills up the inner chamber 5 of the capsule and the fluid is prevented by the blocking member 12 to leave the chamber, the exact volume of the collected body fluid in a sampling capsule can be predetermined. The capsule 2 with the enclosed sample of body fluid 26 is now fed through the gastrointestinal tract and is recovered from the fecies of the patient.

Figure 4 shows the recovered capsule 2 in a state in which the body fluid sample is evacuated from the inner chamber 5 of the capsule. An evacuation needle 28, directly or indirectly connected to an instru-

ment for examination and analysis of the body fluid sample, penetrates the notch 24 of the chamber wall 3 and empties the inner chamber 5.

Figures 5 and 6 show a second preferred embodiment of the invention, which differs from the embodiment of Figures 1 - 4 only in that the inlet of the capsule 2 is designed differently. Several, e.g. four in the shown embodiment, protrusions 30 are disposed externally on the capsule 2 at the inlet opening 18. Between the protrusions 30 laterally directed inlet grooves 32 are formed. The protrusions 30 protect the inlet opening 18 in such a way that they prevent the capsule 2 from being adhered to the walls of the digestive system by the suction forces generated by the internal underpressure. A free flow of body fluid through the inlet grooves 32 into the capsule 2 is thus always secured.

As described above, the capsule 2 consists of two members 4, 6 which are permanently joined together. The members 4, 6 are preferably made of injection-moulded thermoplastic, such as Macrolon® D for example, which is a strong, acid resistant and transparent material and thus suitable for this purpose.

The blocking member 12 is preferably made of an elastic rubbery material and may be injection-moulded. The shape (see for example Figures 3 - 5) and the material properties of the blocking member 12 generate the self-closing function and force the blocking member to bear on and seal off the inlet opening 18 from the inside of the capsule 2.

The sampling device according to the invention is made of a few parts, i.e. the cap member 4 with the plug 20, the body member 6, the blocking member 12 and, when required, also the filter 10. As shown in Figure 7, these parts are fully or partly assembled in a vacuum chamber 40, in which a vacuum or substantial underpressure is maintained by means of a vacuum pump (not shown) connected to the vacuum chamber through the vacuum hose 42. In accordance with the invention, at least the assembly-step that finally seals off the inner chamber 5 of the capsule from the external environment shall be carried out in

the vacuum chamber 40 in order to achieve a vacuum or substantial underpressure in the inner chamber 5, such that sufficient suction forces are generated to force the blocking member 12 to a flow permitting configuration and the body fluid sample to enter and fill the capsule.

5 To assemble the sampling device according to the invention, the blocking member 12 and possibly the filter 10 are initially mounted in the cap member 4 or the body member 6 and subsequently the two members of the capsule are permanently joined together, preferably by ultrasonic welding. The plug 20 may previously have been inserted in
10 the inlet opening 18 of the capsule. In that case, the joining of the two members 4, 6 together, constitutes the assembly-step that seals off the inner chamber 5 of the capsule. Thus, at least this assembly-step must be carried out in the vacuum chamber 40.

Alternatively, when the blocking member 12 and the filter 10 have
15 been mounted in either of the two members 4, 6 of the capsule 2, these two members 4, 6 are permanently joined together, and then the final sealing of the inner chamber 5 of the capsule is made by introducing the plug 20 into the inlet opening 18. Thus, at least this final assembly-step shall be carried out in the vacuum chamber 40. The plug 20, for
20 example made of an organic glue, is quickly set when it is cooled. In the embodiment as shown in Figure 7, the plug 20 is applied by means of a nozzle 44 and the glue is fed into the nozzle from the container 46. In the embodiment of Figure 7, the nozzle 44 initially is inserted into and through the inlet opening 18 of the capsule in the vacuum chamber,
25 such that the elastic and self-closing blocking member 12 is forced by the nozzle 44 to open the communication to the inner chamber 5 of the capsule and the vacuum in the vacuum chamber is transmitted to the inner chamber 5. The nozzle 44 is then withdrawn to the position of the inlet opening 18, where the plug 20 is applied by the nozzle 44 and sets,
30 such that the capsule with its internal vacuum or substantial underpressure is finally sealed. Thus, in this assembly-step, the nozzle 44 is

first used to open the blocking member 12 and subsequently to apply the plug 20 of glue in the inlet opening 18.

The capsule 2 may further be provided with an additional outer, covering film of gelatine or any other suitable material, which is
5 dissolved in the digestive system. The film may be applied in order to minimise the resistance when the capsule is swallowed by the patient.

It will be understood that the invention is not restricted to the
aforedescribed exemplifying embodiments thereof and that several conceivable modifications of the invention are possible within the scope of
10 the following claims. For example, the plug may be formed to be fully dissolved after a predetermined time in the digestive system, such that a time delay of the opening of the inlet opening is obtained. The elastic blocking member may have other forms and shapes and be placed differently in the capsule. Instead of one single inlet opening, as de-
15 scribed in the embodiments above, several adjoining inlet openings may be provided in the capsule. In the description above, only samples of body fluids have been discussed. It should, however, be noted that the sampling device according to the invention also may be used to collect samples comprising gases and/or solid particles in the digestive system.

CLAIMS

1. A sampling device for obtaining samples of internal body substances in the digestive tract of a patient, said device having a shape of a swallowable capsule (2) which allows a sample of the body substance to enter the capsule through at least one inlet opening (18) which is opened in a predetermined position of the digestive tract following contact with the body substance to be collected,

characterised in that the capsule (2) comprises

a capsule wall (3) comprising said inlet opening (18), which initially is sealed and, when the patient has swallowed the capsule (2), is opened in said predetermined position following contact with the body substance to be collected,

an inner chamber (5), defined by said capsule wall (3) and disposed to preserve a vacuum or substantial underpressure when the inlet opening (18) is sealed, and

a blocking member (12) disposed in the inner chamber (5) adjacent to the inlet opening (18) in the capsule wall (3), said blocking member (12) being elastic and having a configuration, such that, when the inlet opening (18) has been opened following contact with said body substance, the blocking member (12) has a flow permitting configuration which admits a flow of body substance into the inner chamber (5) as long as there is a pressure difference between the inner chamber (5) and the external environment of the capsule (2) and a flow preventing configuration which blocks the inlet opening (18) from the inside of the chamber (5) when said pressure difference has been equalised by the flow of body substance into the capsule (2).

2. A sampling device according to claim 1, **characterised** in that the inlet opening (18) is sealed by a plug member (20) of a material that is dissolved following contact with said body substance.

3. A sampling device according to claim 1, **characterised** in that the blocking member (12) consists of an elastic, self-sealing membrane, which in said flow preventing configuration sealingly bears on the inside

of the capsule wall (3), such that an outflow of the body substance in the inner chamber (5) is prevented.

4. A sampling device according to claim 3, **characterised** in that the capsule (2) comprises two members, a cap member (4) and a body member (6), which are permanently joined to each other, and that said blocking member (12) is clamped in the capsule wall (3) between said cap member (4) and said body member (6).

5. A sampling device according to claim 4, **characterised** in that the blocking member (12) is substantially bulb-formed and has at least one laterally located aperture (16) for a through-flow of body substance into the inner chamber (5).

6. A sampling device according to claim 5, **characterised** in that a peripheral edge of the blocking member (12) is clamped between said cap member (4) and said body member (6).

7. A sampling device according to claim 2, **characterised** in that the plug member (20) consists of two or more layers of different materials and that each layer is dissolved in different positions in the digestive tract following contact with a specific body substance.

8. A sampling device according to claim 4, **characterised** in that a filter (10) is clamped between said cap member (4) and said body member (6) for filtrating the body substance that flows into the inner chamber (5).

9. A sampling device according to any of the preceding claims, **characterised** in that protrusions (30) are disposed externally on the capsule (2) circumferentially of the inlet opening (18), thereby forming inlet grooves (32) between the protrusions (30) for securing a free flow of body substance to the inlet opening (18).

10. A sampling method for obtaining samples of internal body substances in the digestive tract of a patient, wherein a capsule (2) is swallowed by the patient and the capsule (2) is opened in a predetermined position of the digestive tract following contact with the body substance to be collected,

characterised in that the body substance is aspirated into the capsule (2) by the force of a vacuum or substantial underpressure inside the capsule and that the body substance is blocked in the capsule (2) by an elastic, self-sealing blocking member (12) disposed inside the capsule (2).

11. A sampling method according to claim 10, **characterised** in that the capsule (2) is opened to collect a sample in that a plug member (20) in an inlet opening (18) in the capsule wall (3) is dissolved following contact with the body substance to be collected.

12. A sampling method according to the claim 11, **characterised** in that said self-sealing blocking member (12) is opened to collect a sample of said body fluid by the force of the vacuum or substantial underpressure in the capsule (2) when the plug member (20) has been dissolved.

13. A sampling method according to claim 12, **characterised** in that said blocking member (12) is blocking the inlet opening (18) from the inside of the capsule (2) when the vacuum or substantial underpressure in the capsule has been equalised.

14. A method for producing a sampling device for obtaining samples of internal body substances in the digestive tract of a patient, said device having a shape of a swallowable capsule (2) which allows a sample of the body substance to enter the capsule through at least one inlet opening (18) in the capsule wall (3) which is opened in a predetermined position of the digestive tracts following contact with the body substance to be collected,

characterised in that the inlet opening (18) in the capsule wall (3) is sealed and/or that the capsule (2), which is made of two permanently joined members (4, 6), is permanently joined in a vacuum chamber (40) preserving a constant vacuum or substantial underpressure, such that a vacuum or substantial underpressure is formed in an inner chamber (5) of the capsule when the inlet opening is sealed and/or when the two members (4, 6) of the capsule are permanently joined together.

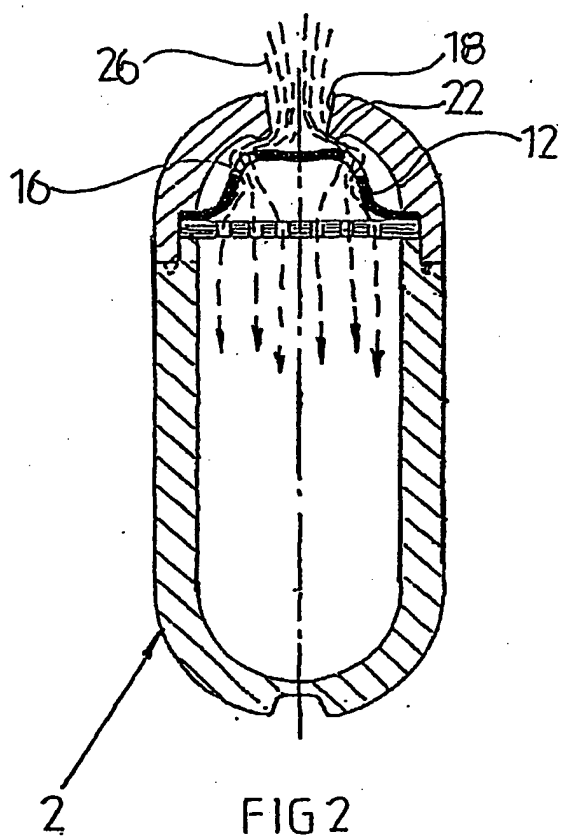
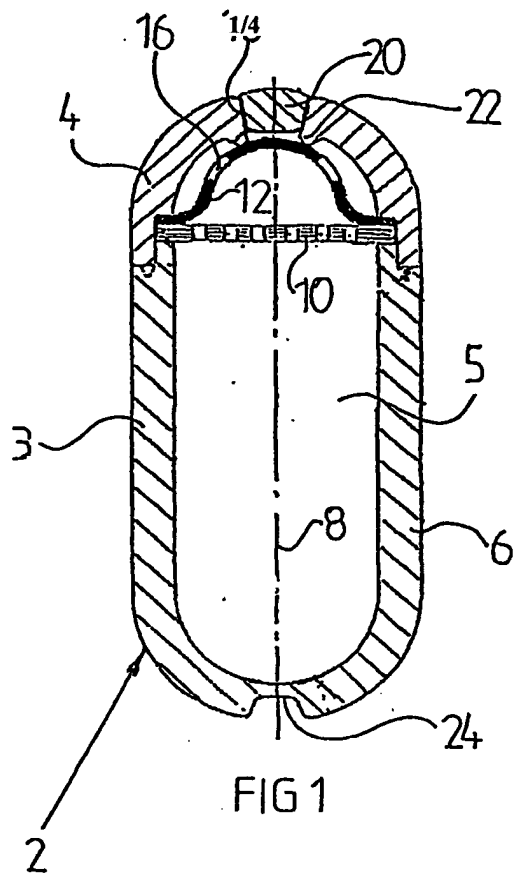
15. A method according to claim 14, **characterised** in that said two members (4, 6) of the capsule are injection-moulded and are permanently joined together, preferably by ultrasonic welding.

16. A method according to claim 15, **characterised** in that an
5 blocking member (12) of the inlet opening (18) is injection-moulded and is mounted between the two members (4, 6) of the capsule prior to permanently joining the two members together.

17. A method according to any of claims 14 – 16, **characterised** in that the inlet opening (18) of the capsule is sealed off by a plug member
10 (20), preferably made of an organic glue, and that the two members (4, 6) are joined together in the vacuum chamber (40).

18. A method according to any of claims 14 – 16, **characterised** in that the two members (4, 6) of the capsule are permanently joined together and that the capsule (2) is sealed off in a vacuum chamber (40)
15 in that a plug member (20) is applied in the inlet opening (18).

19. A method according to claim 18, **characterised** in that applications means (44) for applying the plug member (20), preferably a nozzle, is inserted into and through the inlet opening (18) in the capsule wall (3), that the application means (44) forces the blocking member
20 (12) to open, and that the application means (44) is withdrawn into the inlet opening (18) and the plug member (20), preferably of an organic glue, is applied in the opening (18) by said application means (44).



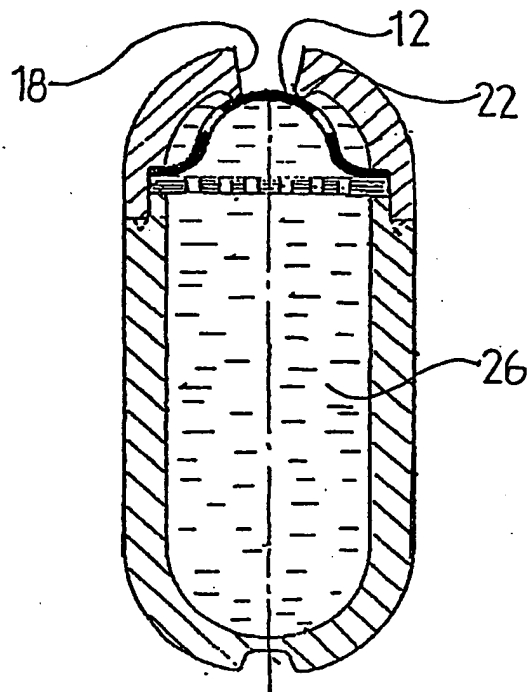


FIG 3

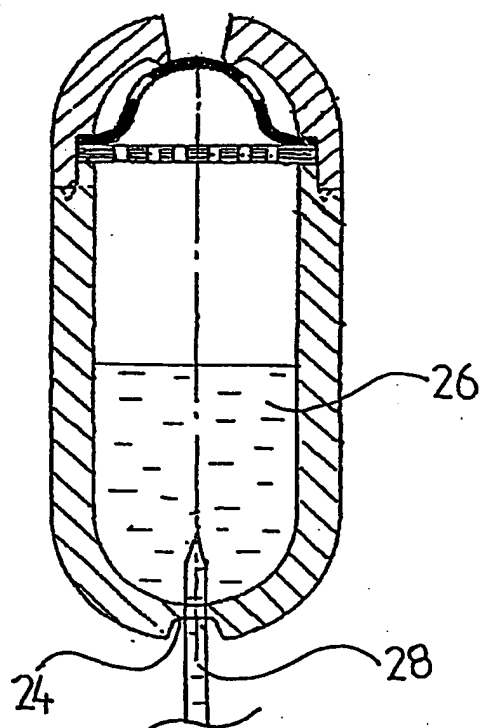


FIG 4

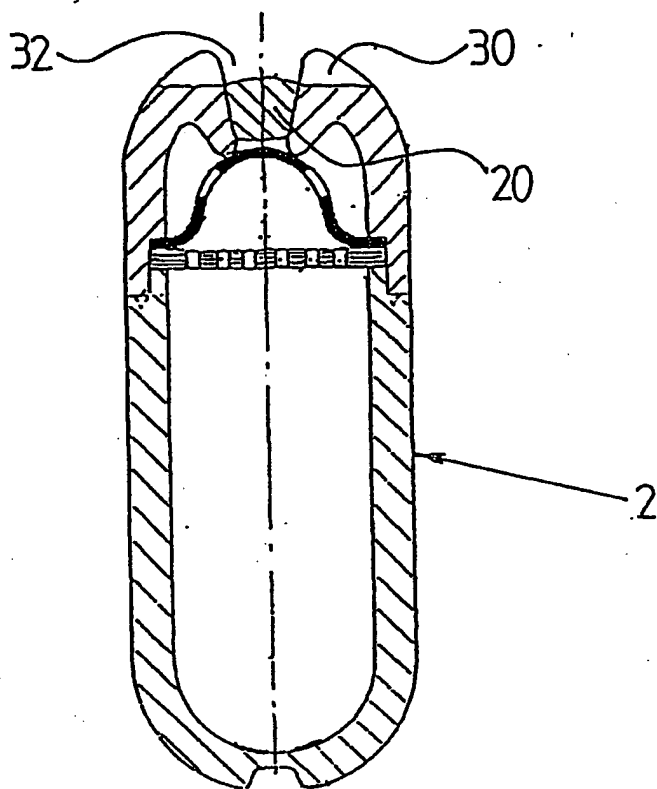


FIG 5

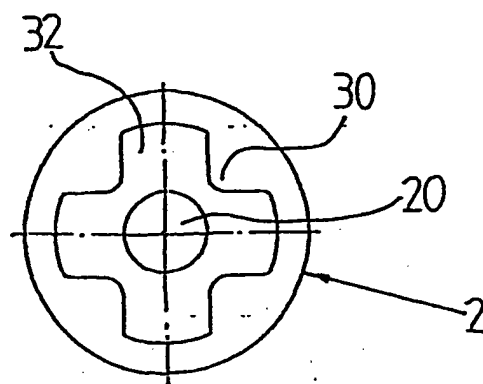


FIG 6

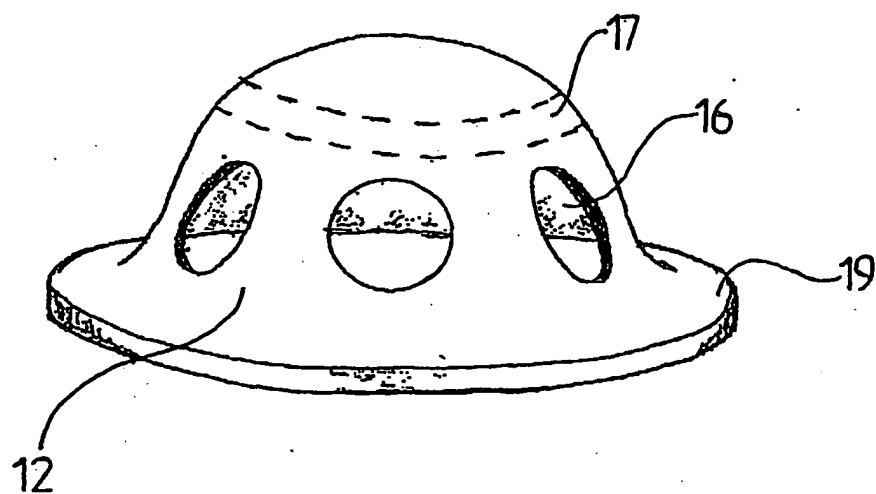


FIG 7

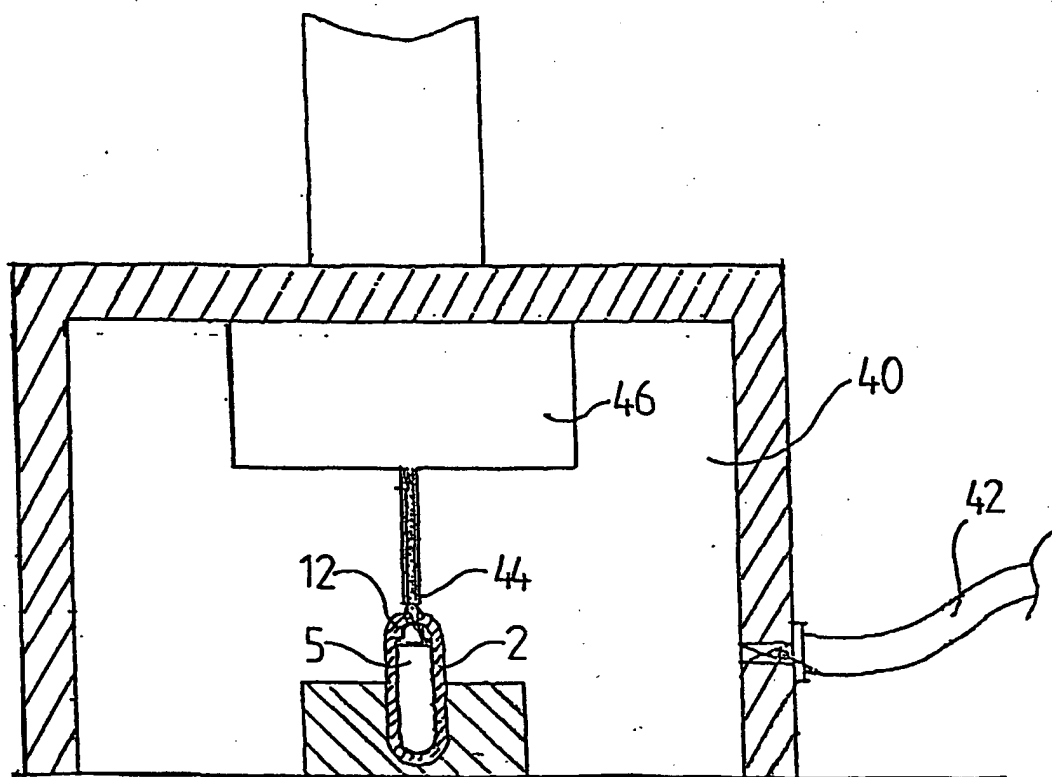


FIG 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00951

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61B 5/00, A61B 10/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61B, A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4481952 A (PAWELEC, J.), 13 November 1984 (13.11.84), column 2, line 38 - line 47; column 4, line 66 - column 5, line 17; column 10, line 8 - line 25, figures 1,15 --	1-19
A	EP 0662304 A1 (THE RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK), 12 July 1995 (12.07.95), column 7, line 39 - column 8, line 6, figures 4,5, abstract --	1-19
A	US 4239040 A (HOSOYA, T. ET AL.), 16 December 1980 (16.12.80), column 2, line 9 - column 4, line 20; column 5, line 64 - column 7, line 10, figures 1,2, 6 --	1-19

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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International application No.

PCT/SE 02/00951

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